REMARKS

Applicant affirms the election made telephonically to prosecute the claims of Group I, i.e. claims 1-17. Claims 18-21 have been canceled without prejudice to their subsequent submission as a part of a divisional or continuing application.

In response to the Examiner's rejection under 35 U.S.C. § 112 (second paragraph), amendments have been made to the claims to more distinctly define what the Applicant considers as his invention. The use of the term "substantial" in claims 1, 3, 7 and 15 has now been qualified as including a segment of nucleic acid containing at least 21 nucleotides. Support for this addition is found at page 15, line 1 in conjunction with the earlier description of the probes as being at least as long as the target material, i.e. the contiguous segment of nucleic acid adjacent to the STR (see page 15, lines 31-35). As is believed clear from the paragraph that begins at line 25 of page 2, the term "FRAXA gene" is intended as referring to the FMR1 gene, i.e. the DNA sequence related to fragile X syndrome. Attached to this paper as Attachments Nos. 1, 2 and 3 are copies of an article from *J. Med Genet 1999*, an abstract of an article from *Human Genetics* (2003) and an article of the Fragile X Research Foundation (2001), all of which use the terms "FRAXA gene", "fragile-X gene" and FMR1 gene interchangeably. The preamble portions of claims 1 and 14 have been amended so as to make it clear that the FRAXA gene is meant to refer to the gene that is more specifically termed the FMR1 gene. Amendments to various of the claims, including claim 16, have been made so as to more specifically recite the oligonucleotide targets which hybridize as a part of step (d), and the oligonucleotide probes which are a part of the microarray and hybridize as a part of step (h).

It is believed that these amendments should satisfy the objections set forth by the Examiner with respect to various of the claims. Thus, it is believed that the rejection under 35 U.S.C. § 112 (second paragraph) should now be withdrawn.

The invention as now defined by amended claim 15 would <u>not</u> be anticipated by the incidental disclosure of U.S. Patent No. 6,268,147 to Beattie et al. (hereinafter Beattie et al.). Beattie et al. disclose methods for detecting the presence of known mutations or DNA sequence polymorphisms using labeled stacking probes which contain a unique sequence on <u>one</u> side of an

STRP plus a set number of repeat units. A hybrid of his tandem probe and nucleic acid being diagnosed will only, very specifically bind to a capture probe attached to a microarray. Binding of target nucleic acid hybrid will only occur when it is hybridized in tandem with one such labeled stacking probe so as to form contiguously stacked labeled probe/capture probe duplex structures. Accordingly, this Beattie et al. technique uses tandem or duplex targets that respectively contain nucleic acid complementary to a portion of the region of interest and a contiguous DNA sequence that flanks the region of interest. When the arrangement is used to detect STRP, as illustrated, for example, in FIG. 14B, there must be precise registration between two such duplex targets/probes. For example, it is stated that where the marker contains 10 repeat units, a capture probe bearing four repeat units would not stack with a hybrid of a stacking probe bearing four repeat units, i.e. such would require a capture probe bearing six repeat units, see column 37, lines 47-62. One signal from the correctly hybridized stacking probes is then detected as part of the analysis.

Applicant's method of invention for detecting STRPs is quite different from the incidental disclosure of Beattie et al. Applicant employs two sets of different, labeled, oligonucleotide targets; they separately target (i) STRs and (ii) the contiguous nucleic acid segment. Then, following hybridization with single-strand DNA that is a product of PCR, the hybridized product is separated, and the labeled target oligonucleotides are recovered from the separated product and then hybridized to a microarray. Thereafter, the colorometric intensities of the separately hybridized target oligonucleotides representing either the STRs or the contiguous nucleic acid segment are measured and compared to determine the ratio of signal intensity at the STR probe regions to the signal intensity at the contiguous nucleic acid segment target regions. It is this ratio which is then used for comparison with known control samples to accurately quantify the number of STRs present in the genomic DNA being tested. Support for the addition to claim 15 that specifies the use of the ratio is found in the definition of the algorithm which appears at page 18, lines 29-37, and on page 20, lines 26-27.

Thus, Applicant's invention employs the reading of two separate colorometric intensities and comparing the ratio between those readings, whereas Beattie et al. is merely looking for a single intensity that would be indicative of a single mutation or STRP. In view of these

significant differences which are now recited in amended claim 15, it is submitted that the rejection under 35 U.S.C. § 102 should be reconsidered and withdrawn. Claims 16 and 17 are dependent upon claim 15 and thus should likewise be allowed.

Claim 1, as amended, would not be obvious from the disclosure of Beattie et al. in combination with the disclosure of the 2002 article from Cytogenetic and Genome Research, authored by Oostra et al. (hereinafter Oostra et al.). Oostra et al., from the standpoint of the present patent application, merely indicate that fragile X syndrome is an inheritable mental retardation trait that results from a full mutation of some 200 to 1,000 CGG repeats in the FMR1 gene. It merely discloses certain consequences and conditions for inheriting this disability. It is unconcerned with detection and in no way alleviates the deficiencies pointed out above with respect to the incidental disclosure of Beattie et al. As a result, it is submitted that claim 1, which likewise includes the recitations to which mention was hereinbefore made with respect to claim 15, in the environment of detecting a mutation indicative of fragile X syndrome, should be likewise allowed, and allowance thereof is respectfully requested. Inasmuch as claims 2-13 are dependent either directly or indirectly upon claim 1, it is submitted that these claims should be likewise allowed.

Moreover, claim 2 recites the specific formula that is used to determine a quantitative number of repeats using the ratio of colorimetric intensities measured and comparing that ratio to such ratios hereinbefore determined based upon subjects with known numbers of CGG repeats. There is clearly nothing in either of the references that would render this recitation obvious. In addition, claims 8, 9, 10 and 11 specify that an anchoring moiety, i.e. biotin, is attached to the forward primer, that separation of the hybridized product is carried out by binding to avidin, that the single-stranded product is obtained by digesting the antisense strand of the double-stranded PCR product with an exonuclease and that the labeled target material is recovered separate from the single-stranded product and then hybridized with the microarray. Accordingly, these claims contain further recitations that are not a part of the incidental disclosure of Beattie et al. where hybrids of the ssDNA and the stacking probes are applied to the microarray.

Independent claim 14 is submitted to be likewise allowable over the combination of the references to Beattie et al. and to Oostra et al. for the reasons set forth with respect to claims 1 and 2. Allowance of this claim is likewise requested.

New claims 22-25 are patterned after claims 1, 2 and 7-14, and are submitted to be allowable for the reasons set forth above with respect to claims 1, 2 and 14. More particularly, both independent claims 22 and 25 are further distinguished from the incidental disclosure of Beattie et al. by reciting that the labeled target oligonucleotides are recovered following their separation from the single-stranded product and hybridized in this form with the microarray. As pointed out hereinbefore, it is a critical feature of the Beattie et al. disclosure that the so-called tandem stacking probes in their hybrids with the single-strand DNA are applied to the microarray.

In view of the foregoing amendments and remarks, it is submitted that claims 1-17 as amended, and new claims 22-25, in the absence of more pertinent prior art, should be allowed, and allowance thereof is respectfully requested. It is believed that this paper should place this application in condition for allowance, and favorable action is courteously solicited.

Respectfully submitted,

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Attachments: Attachment 1: an article from *J. Med Genet* (1999), Attachment 2: an abstract of an article from *Human Genetics* (2003) and Attachment 3: an article of the Fragile X Research Foundation (2001)